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Case Report

Large cell calcifying sertoli cell tumor of the testis: a case report

Ting Lan[1], Hua Zhuang[2], Hongying Zhang[1]

Departments of [1]Pathology, [2]Ultrasonography, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China

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Abstract: Large cell calcifying Sertoli cell tumor is a rare testicular tumor. Here we report the first case of Chinese population in English literature. A 10-year-old boy present with a 4-year history of left testicular enlargement, not associated with Peutz-Jeghers syndrome or Carney complex, and left radical orchiectomy was performed. The clinical, ultrasound, gross, histological, and immunohistochemical features were analyzed. After 15 months of follow-up, there is no evidence of recurrence or metastasis.

Keywords: Large cell calcifying sertoli cell tumor, Leydig cell tumor, differential diagnosis, immunohistochemistry

Introduction

Large cell calcifying Sertoli cell tumor (LCCSCT) is a rare variant of testicular Sertoli cell tumors, and account for 0.4~1.5% of all testicular tumors [1]. It may be associated with hereditary endocrine anomalies such as Carney complex and Peutz-Jeghers syndrome. Histologically, this tumor is characterized by large eosinophilic cells with tubular differentiation, and varying degree of calcifications. In 1980, LCCSCT was firstly reported by Proppe and Scully [2]. Up to now, there have been about 90 cases reported in the literature worldwide. Most examples have been documented as single case reports. To the best of our knowledge, the current case is the first published example of Chinese population in the English literature.

This study focused on characterizing the clinicopathologic features of LCCSCT to promote the recognition of this rare entity for both clinicians and pathologists.

Case report

Clinical findings

A 10-year-old Chinese boy presented with a 4-year history of left testicular enlargement without associated any endocrine anomalies or a familial history. His past medical history and family history was unremarkable. Physical examination revealed an enlarged left testis. There was no evidence of isosexual precocity, gynecomastia, or other stigmata of Carney complex. A scrotal ultrasound revealed a 1.5-cm nodule in the left testis. The mass was characterized by large areas of calcification (**Figure 1**). The impression was unilateral tumor of testis with large areas of calcification. The laboratory results, including α-fetoprotein level were within normal limits. A left radical orchiectomy was performed. At surgery, the patient underwent excisional biopsy with frozen section of the biopsy specimen.

Pathological findings

Gross: The lesion removed from the left testis measured 1.5 cm in largest dimension. It was well-circumscribed and covered by connective tissue. The cut surface revealed an entirely gray-yellow solid mass with scattered calcification. The nodule was solid and homogeneous with no areas of hemorrhage, necrosis, or cystic change.

Light microscopy: In frozen section, the neoplastic cells were very large and had ample eosinophilic cytoplasm. Calcifications were present. Numerous neutrophils were present in the

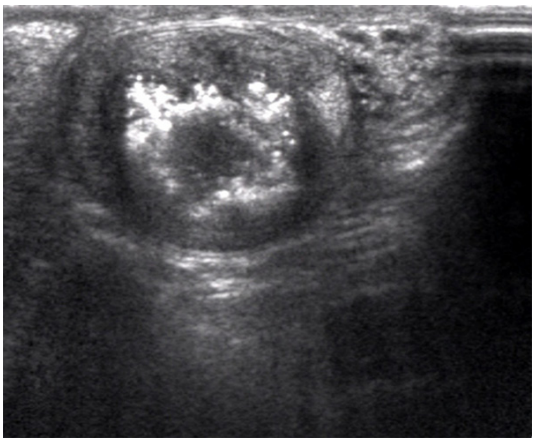

Figure 1. Scrotal ultrasound revealing a mass with large areas of calcification.

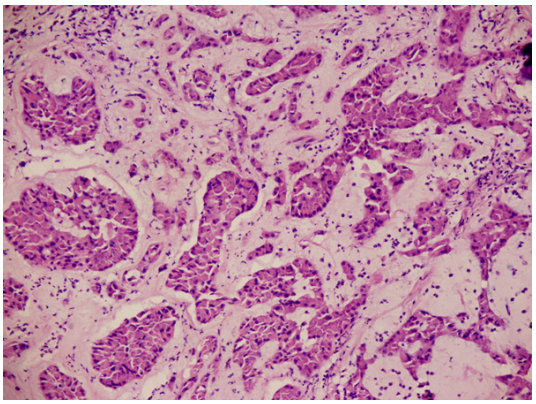

Figure 2. The neoplastic cells form solid and hollow tubules and are immersed in a loose, myxoid matrix (haematoxylin and eosin, ×200).

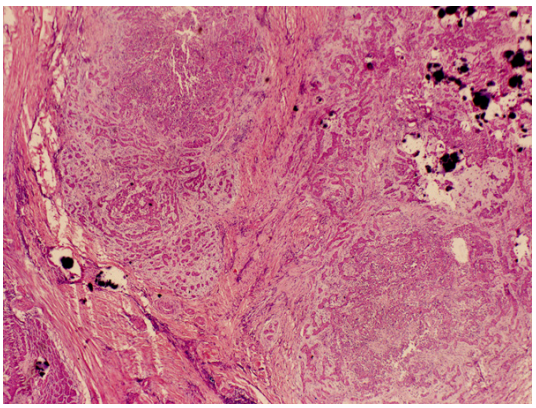

Figure 3. There are scattered calcifications within the lesion. (haematoxylin and eosin, ×40).

tissue between the neoplastic cells. The tumor was considered as sex cord-stromal tumor of left testis on frozen section.

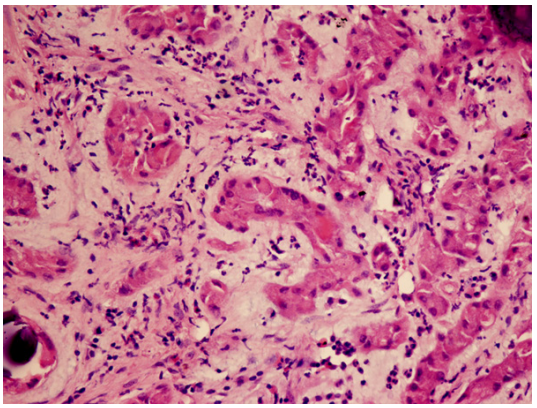

Figure 4. The lesion is composed of large polygonal cells with abundant eosinophilic cytoplasm and eccentric nuclei. Intratubular tumor calcifications are present. (haematoxylin and eosin, ×400).

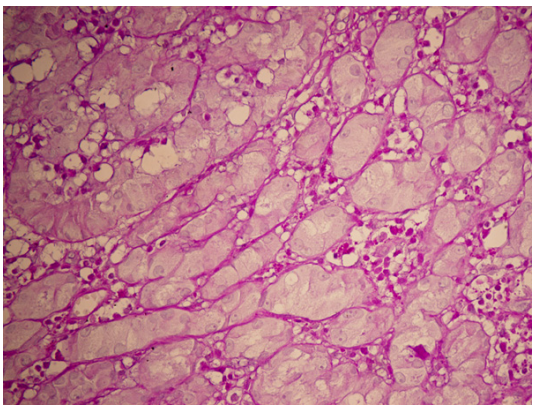

Figure 5. PAS stain is expressed around the tumor cell nests and along the inner luminal surface of the tubular structure (PAS, ×400).

In paraffin section, the lesion was well-circumscribed and surrounded by connective tissue with some lymphoid tissue. The neoplastic cells formed solid and hollow tubules, and nests. The neoplastic cells were immersed in a loose, myxoid matrix that was Acian blue-positive, with large amounts of neutrophilic infiltration (**Figure 2**). There were scattered calcifications (**Figure 3**). The lesion was composed of large polygonal cells with abundant eosinophilic cytoplasm and eccentric nuclei containing single eccentric nucleoli (**Figure 4**). Intratubular tumors associated with lamellar calcifications were prominent. Mitotic figures were very rare. There was no evidence of hemorrhage or necrosis. There was no invasion of the tunica albuginea, the rete testis, epididymis and spermatic cord. The testicular parenchyma uninvolved by the lesion was remarkable.

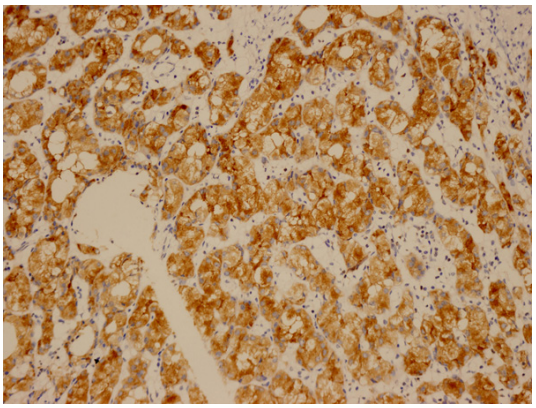

Figure 6. Immunohistochemical stain for inhibin-α showing strong immune reactivity in the tumor cells (×200).

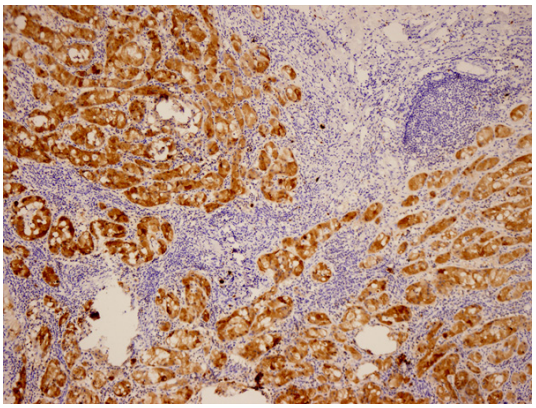

Figure 7. Immunohistochemical stain for S-100 protein showing strong immune reactivity in the tumor cells (×100).

Histochemical and immunohistochemical findings

Alcian blue was expressed in the myxoid stroma. Periodic acid-Schiff (PAS) stain was expressed around the tumor cell nests and along the inner luminal surface of the tubular structure (**Figure 5**). These neoplastic cells strongly express inhibin α (**Figure 6**), S-100 protein (**Figure 7**), calretinin, Melan A, vimentin, and AE1/AE3 and were negative for CK5/6, low-molecular-weight CK, CD99 and EMA. Immunostaining for CD10 was focally positive. Collagen IV and laminin was positive around the tumor cell nests and along the inner luminal surface of the tubular structure. The final pathologic diagnosis is large cell calcifying Sertoli tumor (LCCSCT) of left testis.

Treatment and follow-up

The postoperative course was unremarkable. The boy was discharged and advised to seek further follow-up. Up to now, he has no symptoms 15 months after surgery and no evidence of recurrence or metastatic disease. Of course, clinical follow-up for this patient is ongoing.

Discussion

Sertoli cell tumor is an uncommon subtype of sex cord-stromal tumors. They account for less than 1% of all testicular tumors [3, 4]. There are three subtypes of Sertoli cell tumors including not otherwise specified (NOS) and two variants (sclerosing Sertoli cell tumors and LCCSCTs) [4]. LCCSCT is a rare variant of Sertoli cell tumor. In 1980, Proppe and Scully reported 10 cases of a peculiar Sertoli cell tumor and proposed the name of LCCSCT [2]. There have been a total of about 90 cases reported so far. Importantly, this is the first Chinese case of LCCSCT in English literature. In contrast to Sertoli cell tumors NOS, LCCSCTs are seen most commonly in the second decade of life and the average age is 16 years [4]. Patients harboring LCCSCT typically present with a slowly enlarging testicular mass. LCCSCTs are frequently bilateral and multifocal (40%). About 40% of LCCSCTs may be associated with endocrinologic abnormalities or genetic syndromes [4]. Endocrinologic abnormalities include sexual precocity, gynecomastia, and acromegaly. LCCSCTs may be associated with genetic endocrine anomalies such as Peutz-Jeghers syndrome and Carney complex [5]. Myxomas (heart, skin, breast), spotty pigmentation (lentigines and blue nevi), and endocrine overactivity may be observed in patients with Carney complex [6-8]. Sudden death may happen secondary to cardiac myxomas. Our patient and his family had no clinical signs of Carney complex. Indeed, the diagnosis of LCCSCT prompted us to perform a thorough examination of the patient in the search for other features of the genetic syndrome, particularly a cardiac myxoma, fortunately, cardiac echography was negative. The imaging characteristics of the patients harboring can be specific and distinguishable. Large areas of calcification can be readily seen by ultrasound.

Grossly, the majority of lesions are less than 4 cm in greatest diameter. The lesions are usually

solid and well demarcated. On cut surface, the neoplasms appear gray-yellow or gray-white with gritty nature due to the calcification [9]. Microscopically, the tumor cells have various patterns, such as sheets, nests, ribbons or cords, and small clusters but at least focally solid and hollow tubules are present and often prominent [4, 7]. LCCSCT is characterized by large cells with abundant cytoplasm and tubular differentiation, and laminated irregular calcification [4, 5, 10]. LCCSCT cells mimic those of Leydig cell tumor (LCT) cells in the large, abundant eosinophilic cytoplasm [3, 7, 11]. Mitoses are very rare. Intratubular growth and intratublar calcification can be observed in the lesions. The neoplastic cells are immersed in myxohyaline stroma, often with abundant lymphocytes and neutrophils. Alcian blue is positive in the stroma. PAS can be expressed around the tumor nests and can reveal the basal lamina.

Immunohistochemically, most of these neoplasms are positive for vimentin, inhibin-α, S-100 protein, calretinin, Melan-A, CD10, pan CK, and negative for EMA. Collagen IV and laminin are expressed around the tumor nests and can show the basal lamina [3]. Ultrastructurally, Charcot-Bottcher crystals, composed of filaments, are considered to be typical of Sertoli cell origin but are rarely seen. Sato et al found that the neoplastic cells also showed basal lamina around the tumor nests [3].

The malignancy rate in LCCSCTs is relatively low. Of a total of 90 reported cases, benign LCCSCT outnumber malignant ones 74:16. The benign neoplasms were seen in younger patients (range age, 2-54 years) and multifocal and bilateral (35%). In 36% of the patients, they are associated with an endocrine abnormality or a syndrome [12]. The size of the benign tumors ranges from 0.1 to 5 cm. The malignant neoplasms often present in older patients (range age, 28-73 years) and were rather unilateral and solitary [12]. The size of the malignant counterparts ranges from 2 to 15 cm. Although histological criteria for malignancy in LCCSCT have not been clearly formulated, pathologists should be aware of some features that are useful in determining the behavior of the patients harboring LCCSCTs. Features associated with malignancy are tumor size greater than 5 cm, gross or microscopic necrosis, high-grade cytologic atypia, mitotic rate >3/10HPF, lymphovascular invasion, extratesticular extension (tunica albuginea, epididymis, spermatic cord) [10, 13, 14]. Malignant neoplasms readily metastasize to the retroperitoneal lymph nodes, and rarely hematogenous spread to the liver, bone, and lungs [15].

In the differential diagnosis, based on the microscopic findings, several lesions should be considered especially Leydig cell tumors. Leydig cell tumors have a yellow-white color on cut surface. Microscopic findings of LCCSCT cells resemble those of Leydig cell tumor cells in the large and abundant eosinophilic cytoplasm. Furthermore, both neoplasms can show varying degrees of positivity for some immunohistochemical markers such as vimentin, inhibin-α, S-100 protein, calretinin, Melan-A, CD10, and pan CK. Therefore, many of LCCSCTs might have been misdiagnosed as Leydig cell tumors [3, 16]. The presence of calcifications in the lesions should serve as a useful clue in the distinction between these two tumors. True tu bular formation, intratubular growth pattern, and intratumoral calcification favor a LCCSCT, whereas lipofuscin and Reinke crystalloids can be seen in Leydig cell tumors [2]. PAS staining, collagen IV, and laminin are helpful in revealing the basal lamina in Sertoli cell tumors, but only on the network of Leydig cell tumors [3]. In fact, in our study, the initial impression of this patient was Leydig cell tumor because of the large and eosinophilic cells. The specimens were reexamined by histopathologists with specialist interesting in genital tumors in our hospital by further investigations. A final diagnosis of LCCSCT was made. Tanaka et al and Sato et al have suggested some utility in differentiating these lesions by S-100 protein subunit expression. In their studies, S-100 β expression was seen in Sertoli cell tumors but not in Leydig cell tumors [3, 16]. Besides Leydig cell tumors, tumors of adrenogenital syndrome should be considered. These tumors are also usually bilateral. However, most of the patients may present with the salt-losing form of adrenogenital syndrome [4, 14]. Therefore, we should keep in our mind that clinical information is valuable in reaching the correct diagnosis.

The treatment for unilateral LCCSCT has traditionally been radical orchiectomy [10]. However, some authors recommended partial orchiecto-

my especially for those patients with bilateral tumors [17, 18]. Without adequate long-term follow-up on most cases, the efficacy of testis-sparing surgery versus radical orchiectomy remains an unsettled. Recently, aromatase inhibitors are tested to relieve the symptoms due to Peutz-Jeghers syndrome and Carney complex [5].

In conclusion, LCCSCT is a rare, but distinct variant of Sertoli cell tumors. It is characterized by large eosinophilic cells with tubular differentiation, and varying degrees of calcification. The results of histochemical, immunohistochemical and ultrastructural examinations for basal lamina as well as immunostaining for S-100 protein-β is helpful in distinguishing between LCCSCTs and LCTs. The diagnosis of LCCSCT should prompt a clinical investigation for other stigmata of Carney complex because sudden death may occur secondary to cardiac myxomas. Appropriate long-term follow-up is required for LCCSCTs.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hongying Zhang, Department of Pathology, West China Hospital, Sichuan University, Guoxuexiang 37, Chengdu 610041, Sichuan, China. Tel: 086-28-85423847; Fax: 086-28-85422698; E-mail: hy_zhang@scu.edu.cn

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